Title	Dosage Effects of Histamine-2 Receptor Antagonist on the Primary Prophylaxis of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Associated Peptic Ulcers: A Retrospective Cohort Study
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Dosage effects of histamine-2 receptor antagonist on the primary prophylaxis of non-steroidal anti-inflammatory drug (NSAID)-associated peptic ulcers: a retrospective cohort study

Running title: Dosage effects of H2RA on prophylaxis of NSAID-associated PUs

Keywords: histamine-2 receptor antagonist (H2RA), non-steroidal anti-inflammatory drug (NSAID), peptic ulcer (PU)

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Abstract

Background Histamine-2-receptor antagonist (H2RA) is one of the common gastroprotective co-therapies with non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention or treatment of peptic ulcers (PUs).To date, no study has directly compared the prophylactic effectiveness between high-dose and low-dose H2RA.

Objective To compare the effectiveness of high-dose versus low-dose H2RAs in the primary prophylaxis of PUs among short-term NSAID users.

Methods A retrospective cohort study was conducted using the Clinical Data Analysis and Reporting System (CDARS) in Hong Kong. Patients aged 18 years or above who received a single prescription of oral NSAID with oral H2RA were identified within the study period (1 January 2009 to 31 December 2012). Patients with a history or risk factors for PU in the corresponding two years prior to the index date (of the first NSAID prescription) were excluded. Log binomial regression analysis was used to calculate the relative risk of PU among NSAID users on high-dose-H2RA versus low-dose-H2RA exposure.

Results Among the NSAID cohort (n=102 042), 77 509 (76%) were on low-dose-H2RA and 24 533 (24%) were on high-dose-H2RA. Of the total 69 PU cases identified during the drug exposure period, 64 (0.08%) received low-dose-H2RA and 5 (0.02%) received high-dose-H2RA. The overall absolute risk of PUs for NSAID users whilst on H2RA was approximately 1 per 1 479 patients. The adjusted relative risk for NSAID users receiving high-dose-H2RA versus low-dose-H2RA was 0.32 (95% Confidence interval 0.13 to 0.79). Patients aged ≥65 years, on longer duration of treatment, or concomitant use of antiplatelet agents were found to be at higher risk of PU.

Conclusion High-dose-H2RA showed greater effectiveness than low-dose-H2RA in the primary prophylaxis of NSAID-associated PUs in short-term new-users.

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Key Points:

- The effectiveness of high-dose and low-dose histamine-2 receptor antagonists for the prevention of peptic ulcers has not been directly compared.
- The absolute risk of peptic ulcer among non-steroidal anti-inflammatory drug new-users with concurrent use of histamine-2 receptor antagonists was approximately 0.07%, and the incidence rate was approximately 11.4 per 1000 patient-years.
- High-dose histamine-2 receptor antagonist showed greater effectiveness than its low-dose form in the primary prophylaxis of NSAID-associated PUs in short-term new-users.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed treatment used for pain relief, fever and rheumatic disorders such as rheumatoid arthritis, osteoarthritis, acute gout, and other inflammatory pain management [1-3]. However, as NSAIDs inhibit the production of prostaglandins and increase gastric acid secretion [4], their potential to cause peptic ulcers (PUs), including gastric and duodenal ulcers, remains a major concern [5]. A previous study showed that the baseline incidence of hospitalisation with upper gastrointestinal event in patients receiving NSAIDs was about 2% [6]. In addition, several risk factors for NSAID-associated PUs are well-documented, including prior history of gastrointestinal events, aged 65 years or older, high dose NSAID, and concurrent use of corticosteroids, anticoagulants and antiplatelet agents [7]. Gastroprotective agents (GPA) such as histamine-2-receptor antagonist (H2RA), proton pump inhibitor (PPI) and misoprostol are commonly prescribed together with NSAIDs for the treatment or prevention of PUs [8-12].

A Cochrane review reported that both standard-dose H2RA (ranitidine 300mg/day or famotidine 40mg/day) and high-dose H2RA (ranitidine 600mg/day or famotidine 80mg/day) were effective compared with placebo in the prevention of NSAID-associated endoscopic PUs (i.e. peptic mucosal lesion observed under endoscopy [13]). The relative risk (RR) for standard-dose H2RA was 0.63 (95% Confidence Interval 0.45 to 0.88) and 0.41 (95% CI 0.26 to 0.63) for high-dose H2RA. As the 95% CI overlapped in this indirect comparison, it is unclear whether high-dose H2RA is indeed more effective.

We were unable to identify any published head-to-head study comparing high-dose versus standard-dose H2RA, as all data were based on indirect comparisons. Therefore, it is difficult to draw conclusions on the effectiveness of different doses of H2RAs in preventing NSAID-associated PUs. Most of the clinical trials investigating NSAID-associated PU prophylaxis/treatment included patients with a previous history of PU, i.e. secondary prophylaxis. For instance, all the patients

included in Wolde *et al*'s study had a history of ulcer [14]. Hudson *et al*'s study included 28% and 31% of patients with previous ulcers in the placebo and H2RA treatment group, respectively [15]. It is still unclear how effective different doses of H2RA are in primary prophylaxis. Finally, it has been argued that many endoscopic ulcers may, in fact, be asymptomatic with no clinical symptoms [13,16, 17], which are different from clinical ulcers (i.e. symptomatic ulcers or ulcer complications). In addition, Yeomans *et al* demonstrated the difficulty with using endoscopic PU as an outcome in that a standard-dose H2RA (ranitidine 300mg/day) group was almost 3.5 times more likely to develop endoscopic PU than the PPI group. However, Yeomans' study also reported no difference between PPI and standard-dose H2RA in preventing clinical PUs [18]. These debates reveal a "translational evidence gap" in the randomised control trial results and the clinical practice. Therefore, investigating the effectiveness of different doses of H2RA in preventing NSAID-associated PU in real-life practice becomes an important public health issue in places like Hong Kong, where H2RAs are the main prophylactic treatment prescribed [19].

The objective of our study therefore was to investigate the absolute risk and incidence rate of clinical PUs among NSAID users whilst on H2RA and, to compare the effect of high-dose versus low-dose H2RA in the primary prophylaxis of NSAID-associated PUs in short-term users.

2. Methods

2.1. Data sources

In this study, we used the Clinical Data Analysis and Reporting System (CDARS), a database developed by the Hong Kong Hospital Authority (HA). The HA is a statutory body which manages all publicly-funded hospitals and their ambulatory clinics (primary and specialist out-patient) in Hong Kong [20]. Prescriptions obtained from HA ambulatory clinics must be dispensed by HA pharmacies because community pharmacies do not dispense HA prescriptions. As a publicly-funded primary, secondary and tertiary healthcare provider, the HA's health service is available to all Hong Kong residents (over 7 million people) [21].

In 1995, the HA developed Clinical Management System (CMS). The CMS is a computerised clinical management system which allows clinicians to order, document and review patient care through an electronic patient record. Patient data are recorded in CMS by trained clinicians, and typically include basic demographics, diagnosis, payment method, prescriptions, laboratory tests, admissions and discharge information, which are directly transferred to CDARS. Only trained clinicians are able to prescribe through CMS, where the drug name, dose and frequency are stored. Prescriptions are forwarded to the corresponding pharmacy department and verified by a registered pharmacist who dispenses the drugs.

CDARS contains the records of all in-patients and out-patients attending HA clinics and hospitals, including data transferred from the Accident and Emergency Information System, Medical Record Abstract System, In-Patient Administration System, Pharmacy Management System/Corporate Drug Dispensing History. Patient records are anonymised (name, Hong Kong identification card number, address and telephone number are withheld) to maintain confidentiality. A reference number is generated to facilitate data retrieval and further analysis. CDARS contains clinical data from 42 public hospitals and institutions via seven geographic clusters in Hong Kong [22] and has been used in several high quality epidemiological studies [23-26].

2.2. Study Design

This is a retrospective cohort study to investigate the dose effect of H2RA in NSAID users with respect to the clinical outcome of PU.

2.3. Patient identification

An inception cohort of patients aged 18 years or above prescribed NSAIDs with H2RA issued by the ambulatory clinic between 1 January 2009 and 31 December 2012 (study period) was retrieved from the CDARS database. The NSAIDs and H2RAs included in the HA formulary are shown in **Table 1**. We defined the date of the first NSAID prescription during the study period as the index

date. We specifically selected patients with only one prescription for consistency in the setting of numerous clinical possibilities including treatment course definition of multiple NSAID prescriptions and switching between NSAIDs.

2.4. Exclusion criteria

Patients with unknown date of birth, gender, prescription information, or with multiple or non-oral NSAID prescriptions during the study period were excluded. To obtain a new-user cohort, those who had received NSAIDs within the screening period (2 years prior to the index date) were excluded. Further, patients with a previous diagnosis of PU or *Helicobacter pylori (H. pylori)* infection, received triple therapy for *H.pylori* eradication (**Table 1**) or gastrointestinal endoscopy procedure during the screening period were also excluded. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes used for identifying diseases and procedures are listed in **Table 2**. The flowchart **in Figure 1** illustrates patient inclusion and exclusion.

2.5. Definitions of Exposure

Based on the British National Formulary (63^{nd} edition),[27] high-dose H2RA was defined as double-dose or higher, and low-dose was defined as lower than double-dose (including standard-dose) **(Table 3)**. The drug exposure period was defined as the prescription period in which patients were concurrently prescribed NSAID with H2RA. The observation was censored by the end of the prescription, diagnosis of PU, prescription of another GPA (e.g. PPI, misoprostol), death or end of study period (31 December 2012), whichever was earliest.

2.6. Outcome

The outcome of interest in this study was PU within the drug exposure period during 2009-2012. PU diagnoses were identified from the primary diagnostic codes (ICD-9-CM 531, 532, 533 and 534) (**Table 2**), including acute or chronic peptic ulcers with or without mention of haemorrhage or

perforation. Ninety-six percent of the PU cases were confirmed with GI endoscopy, GI surgery or related diagnostic procedures (**Table 2**). All PU cases were confirmed with a record of hospital admission. Only the first episode of PU was counted and observation was censored thereafter.

2.7. Covariates

The commonly reported risk factors for PU were considered in our study as covariates: age ≥65years; concomitant use of corticosteroids, anticoagulants or antiplatelet agents (**Table 1**); NSAID types (ibuprofen, diclofenac, naproxen and others); NSAID doses (low, medium/high) and duration of NSAID exposure [6, 28]. Based on the British National Formulary (63nd edition) and existing literature [27, 29, 30], the dose of NSAID was categorised into low and medium/high dose (**Table 3)**.

2.8. Statistical Analysis

The adjusted RR of PU in NSAID users receiving high-dose versus low-dose-H2RA and corresponding 95% confidence intervals were estimated using log-binomial regression. The effect of age, gender and other covariates mentioned previously were also analysed.

The crude absolute risks (AR) and incidence rates (IR) of experiencing PU in comparative groups and overall patients were calculated based on the following equations:

$$\text{crude absolute risk (AR)} = \frac{Number\ of\ patients\ diagnosed\ with\ PU\ within\ the\ observation\ period}{\text{Total number of patients}}$$

$$\text{crude incidence rate (IR)} = \frac{Number\ of\ new\ PU\ cases\ within\ the\ observation\ period}{\text{patient years at risk } within \text{ the observation period}}$$

The Wilson score interval was used to calculate the corresponding 95% confidence interval for the AR [31]. The 95% confidence interval of IR was calculated based on Rothman and Greenland's method [32].

The number needed to treat (NNT) was calculated to illustrate the observed effect size using the equation NNT=1/(risk among low-dose-H2RA users with PU – risk among high-dose-H2RA users with PU) [33].

2.9. Sample size calculation

Kelsey *et al*'s method was used to calculate the sample size required [34]. Assuming that the background incidence of hospitalisation with PUs is approximately 2% [6], a minimum sample size of 6 223 and 18 668 patients in each arm is required respectively, in order to detect a RR of 0.65 comparing high-dose versus low-dose-H2RA (the RR from Rostom *et al*) [17] with 80% power (two-sided 95% CI).

2.10. Sensitivity and subgroup analyses

Three sensitivity analyses were performed to test the robustness of the study results. The first analysis addressed issues around the delayed effect of drug exposure and development of PU, as well as potential non-compliance scenarios by extending the follow-up period for 30 days. The second analysis included any PU diagnosis as an outcome instead of restricting them to diagnosis during hospitalisation, to assess whether the inclusion of out-patient diagnosis would affect the conclusion. The final sensitivity analysis excluded any PU diagnosis without confirmation with GI endoscopy, GI surgery or related diagnostic procedures.

Subgroup analysis was also performed to estimate the RR of high-dose versus low-dose H2RA in three groups of patients separately; elderly patients (aged 65 or above), and patients with longer treatment duration (30-60 days, or over 60 days).

Data analyses were performed using Statistical Analysis System (SAS) version 9.3 (SAS Inc., United States). A significance level of 5% was used in all statistical analyses.

3. Results

3.1. Patient characteristics

Between 2009 and 2012, a total of 102 042 patients with a single prescription of oral NSAID with co-prescription of H2RA met the inclusion criteria (**Figure 1**). Of these patients, 77 509 (76.0%) were on low-dose-H2RA (32 751, 42.3% male), and 24 533 (24.0%) were on high-dose-H2RA (10 463, 42.6% male).

Patient characteristics by exposure group of different doses of H2RA are detailed in **Table 4**. Over 99.9% of patients were prescribed famotidine in clinical practice in Hong Kong. More than 20% of patients were aged 65 years or older. Over 70% of patients were on medium or high dose NSAID in both treatment groups. In NSAID users receiving low-dose-H2RA, the most commonly prescribed oral NSAID were diclofenac, followed by naproxen and ibuprofen; while diclofenac, ibuprofen and naproxen were the most commonly prescribed NSAID in the high-dose-H2RA group. In both groups, less than 10% of patients were concurrently prescribed corticosteroids, anticoagulants or antiplatelet agents respectively. Over 80% of the NSAID prescriptions were of short duration (i.e. less than 1 month) in both treatment groups, with a mean duration of 23 and 18 days in low-dose-H2RA and high-dose-H2RA groups respectively.

3.2. Crude absolute risks and incidence rates of PU hospitalisation

The ARs and IRs of PU are shown in **Table 5**. A total of 69 PU cases were identified during drug exposure in the study cohort, in which 64 patients received low-dose-H2RA and 5 received high-dose-H2RA. The AR of PU whilst on low-dose-H2RA in NSAID users was 0.08% (0.06% to 0.11%), and the AR was 0.02% (0.01% to 0.05%) whilst on high-dose-H2RA. The overall AR of PU was 0.07% (0.05% to 0.09%), approximately 1 per 1 479 patients.

The IR of PU in NSAID users whilst on low-dose-H2RA was 13.3 per 1000 patient-years (10.4 to 17.0), whereas the IR was 4.1 per 1000 patient-years (1.7 to 9.9) whilst on high-dose-H2RA. The overall IR of PU in these NSAID users was 11.4 per 1000 patient-years (9.0 to 14.5).

3.3. Number needed to treat

The number needed to treat to prevent PUs among NSAID users in Hong Kong would be 1/ [(64/77 509)—(5/24 533)] =1 608, if the estimated effect was seen in a randomised trial. We estimated that an average of 48 cases of PU could have been prevented if all patients were given high-dose H2RA during the study period.

3.4. Adjusted relative risk of PU hospitalisation

The adjusted RR of PU comparing high-dose-H2RA versus low-dose-H2RA in NSAID users was 0.32 (0.13 to 0.79), indicating the superior effectiveness of high-dose-H2RA in preventing NSAID-associated PUs in this study population (**Table 6**).

Patients aged 65 years or above showed a significantly higher risk of experiencing PU with a RR of 11.84 (6.34 to 22.14) compared to those under 65 years old. Moreover, the risk of PU was significantly higher in patients with longer treatment duration. Compared to short-term treatment (less than 1 month), the respective RR was 3.94 (2.06 to 7.55) for 30-60 days treatment and 4.76 (2.75 to 8.23) for treatment longer than 2 months.

Patients receiving concurrent antiplatelet agents showed a significantly higher risk of PU than those who did not, with a RR of 1.85 (1.08 to 3.17).

Our results also demonstrate that female and male patients receiving NSAID plus H2RA showed a similar risk of PU, with a RR of 0.69 (0.43 to 1.11). In addition, there was no significant difference in PU risk for patients receiving different doses or types of NSAID.

3.5. Sensitivity and Subgroup analyses

All sensitivity analyses yielded similar results to the main analysis (**Table 6**). In terms of subgroup analysis, there were 24 117 patients aged 65 or above, 7 469 patients with 30-60 days of treatment and 8 469 patients with over 60 days of treatment. Subgroup analysis showed that among elderly

patients, high-dose-H2RA was able to significantly lower the PU risk compared to low-dose-H2RA, with a RR of 0.36 (0.15 to 0.91) (**Supplementary Table 1**). High-dose-H2RA users of longer duration (30-60 days or over 60 days) were less likely to experience PU than low-dose-H2RA users; however, the results were not statistically significant.

4. Discussion

4.1. Comparisons with other studies and implications of results

Indirect comparison from the Cochrane meta-analysis shows that high-dose H2RAs are not significantly more effective than low-dose H2RAs in the prophylaxis of endoscopic PUs [17]. To our knowledge, our study was the first to demonstrate that the risk of clinical PU was significantly lower among new NSAID users prescribed with high-dose compared to low-dose-H2RA. H2RAs suppress both the basal and stimulated acid secretion by blocking histamine type-2 receptors on the parietal cells, therefore serving as gastroprotective agents commonly used for prophylaxis or treatment of NSAID associated PU. As an inverse agonist and competitive antagonist of histamine, the dose-dependent effect of H2RAs may be the reason that high-dose H2RA has higher efficacy for the prophylaxis of NSAID-associated PU [35-37].

Current guidelines recommend that for patients at high (e.g. prior PU or with more than two gastrointestinal (GI) risk factors) or moderate risk (one to two GI risk factors) of PU, NSAID plus misoprostol or PPIs should be used rather than H2RAs [28, 38, 39]. However, Ho *et al* reported that of the NSAID users who developed ulcer bleeds while on GPA prophylaxis, approximately 80% received H2RA rather than PPI in Hong Kong [19]. The choice of H2RA over PPI is likely to be influenced by the fact that PPI costs up to 30 times more than H2RA in Hong Kong. A pharmacoeconomics study conducted by Brown *et al* also concluded that the optimal strategy for PU prophylaxis in NSAID-users depends on 'willingness-to-pay' and co-therapy with H2RAs is the least costly strategy [40]. Another economic analysis even suggested H2RAs be co-prescribed to all NSAID users for ulcer prophylaxis, especially among patients with low- to average-PU risk [11].

To date, H2RAs are much more commonly prescribed than PPIs in Hong Kong due to cost constraints, whereas studies report that PPI prescriptions have overtaken that of H2RAs in NSAID users in other countries such as Australia, Netherlands and Spain [41-43].

However, our results showed that among the NSAID users concurrently receiving H2RAs, 76% received low-dose-H2RA as primary prophylaxis for PU compared to 24% of patients receiving high-dose H2RA. This might be of concern for clinical practice in Hong Kong, since high-dose H2RA should be preferred given the evidence of greater prophylactic effect compared to low-dose [8]. Although the choice of H2RAs for PU prophylaxis among NSAID users is, to some extent, reasonable in Hong Kong, high-dose-H2RA should be prescribed over low-dose-H2RA.

The overall AR of PU in users prescribed NSAID with H2RA was 69 per 102 042 patients (0.07%), which is much lower than that reported in the literature [6, 44]. The most probable explanation for this low absolute PU risk is due to the "new-user" and "new-patient" design of our study. Since patients with prior PU, NSAID/GPA exposure, *H. pylori* infection or previous GI endoscopy procedures at the screening period were excluded; it is not surprising that PU risks among these new patients are much lower.

In line with previous studies, our results showed that patients aged 65 or above posed a significantly higher risk of NSAID-associated PU with a RR of 11.84 (6.34 to 22.14). Further, longer NSAID treatment duration led to an approximately 3-4 fold higher risk of PU. Subgroup analysis showed the greater protective effect of high-dose compared to low-dose H2RAs in the elderly subgroup. High-dose-H2RA users of longer duration (30-60 days or over 60 days) were also less likely to experience PU than low-dose-H2RA users; however, the results did not reach significance possibly due to the low number of patients with PU in the subgroup. Nevertheless, these findings highlight the importance of an appropriate approach to PU prophylaxis in clinical practice among elderly NSAID users. Shorter NSAID treatment duration is preferred and high-dose H2RAs should be used for PU prophylaxis.

Previous studies and guidelines have stated that concurrent use of corticosteroids, anticoagulants or antiplatelet agents are well-established risk factors for NSAID-associated GI events [28, 45-47]. Our results show that concomitant use of antiplatelet agents resulted in a higher risk of clinical PU among NSAID users despite the dosage of H2RA. However, there was no significant difference in PU risk between patients with and without concurrent treatment of corticosteroids or anticoagulants. The study is not adequately powered to detect the difference possibly due to the scant number of PU cases and small proportion of concomitant use of these drugs (less than 10% respectively) among these new-users of NSAID plus H2RA.

MacDonald *et al* reported that patients receiving medium or high dose NSAID had a higher risk of developing complicated GI events, with RRs of 1.41 (1.03 to 1.93) and 1.92 (1.18 to 3.14) respectively. However, medium or high dose NSAIDs posed similar risks for overall GI events compared to low dose NSAIDs, with RRs of 1.25 (0.98 to 1.58) and 1.39 (0.93 to 2.07) [6]. From our findings, a slight tendency was also shown towards a non-significant higher risk of PU in patients receiving medium/high dose NSAIDs, with a RR of 1.05 (0.37 to 2.94). In addition, MacDonald *et al* showed that compared to ibuprofen, the RR of upper GI adverse event was 1.35 (0.69 to 2.62) among diclofenac users and 1.44 (0.92 to 2.45) among naproxen users [6]. Our results also demonstrated that diclofenac and naproxen had a statistically non-significant higher PU risk compared to ibuprofen.

4.2. Strengths and limitations of study

To our knowledge, this is the first pharmacoepidemiological study comparing high-dose versus low-dose H2RA in the prophylaxis of NSAID-associated PU. One major advantage of our study is that the diagnosis of PU was identified by ICD-9-CM diagnostic codes as an outcome rather than endoscopic PU commonly used in clinical trials. Therefore, our study adds significant knowledge to the role of H2RA in the prophylaxis of NSAID-associated PU in real life practice. Further, we chose the "new-user" [48] and "new-patient" study design, which focused on the primary

prophylaxis of PU in patients with no previous drug exposures or PU history. This allowed us to specifically investigate new-users with low risk of PU, contributing important knowledge to guide current practice. By applying the new-user design, as all subjects enter the study at the same time with no previous drug exposures or outcomes, "survival bias" is avoided, providing a more accurate estimation of risk [48].

Several limitations should be acknowledged. Similar to databases from clinical healthcare management systems in Europe, such as the Clinical Practice Research Datalink (CPRD, previously known as the General Practice Research Database, GPRD)[49], CDARS does not include over-the-counter (OTC) medicines and data from private healthcare providers. This might have led to a potential underestimate of NSAID or GPA use among the study population. However, as the Hong Kong Hospital Authority provides territory-wide healthcare, which is available to all residents, the impact of missing private or OTC prescriptions is likely to be minimal [50]. Similar to other pharmacoepidemiological studies using databases, since we used the prescription record as a reflection of drug exposure, non-adherence cannot be directly addressed. However, we addressed this issue using sensitivity analysis and our conclusions are robust. There is a possibility that patients who were "perceived" to be at higher PU risk might have been prescribed high-dose H2RA. Therefore, our study might be biased against high-dose H2RA and underestimated its protective effects. Finally, we focused on a group of short-term users who received a single prescription for NSAID, thus our findings may not be generalised to other patients groups, such as those on long-term NSAID treatment. Further investigation involving patients with multiple NSAID prescriptions for long-term conditions/treatment using propensity score could be conducted to evaluate different patient groups.

5. Conclusion

High-dose H2RA showed greater effectiveness compared to low-dose H2RA in the primary prophylaxis of PU in short-term new-users of NSAIDs. The co-prescribing rate of low-dose H2RA

was 3-fold that of high-dose H2RA for the primary prophylaxis of NSAID-associated PUs in Hong Kong, and such practice should be discouraged.

Authorship

Guarantor of the article: YH, EWC and ICKW.

YH, EWC and ICKW contributed to the conception, development and design of the study. YH reviewed the literature. YH, KKCM and WCYL contributed to the analysis of data. YH, EWC, KKCM, WCYL, WKL, LMH and ICKW contributed to the interpretation of data. YH drafted the article. EWC, KKCM, WCYL, WKL, LMH and ICKW revised it critically for important intellectual content. EWC and ICKW provided oversight over all aspects of this study. All authors had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of data analysis. All authors provided final approval of the version to be published.

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Tables

Table 1. List of drugs included in this cohort study

Drug classification	List of drugs
NSAID	Diclofenac, ibuprofen, indomethacin, mefenamic acid, naproxen, piroxicam, sulindac
H2RA	Ranitidine, famotidine, cimetidine
PPI	Pantoprazole, lansoprazole, esomeprazole, omeprazole, rabeprazole
Other GPA	Misoprostol, sucralfate, tripotassium dicitrato bismuthate, bismuth subcitrate, bismuth subnitrate, bismuth carbonate, bismuth + iodoform
Triple therapy	Pantoprazole/lansoprazole/esomeprazole/omeprazole/rabeprazole/ranitidine(bismuth) + amoxicillin + clarithromycin
Corticosteroid	Betamethasone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone acetonide
Anticoagulant	Enoxaparin, heparin, nadroparin, protamine sulphate, tinzaparin, warfarin, dabigatran
Antiplatelet agent	Aspirin, aspirin+glycine, dipyridamole, abciximab, clopidogrel, eptifibatide, prasugrel, aggrenox, ticlopidine

GPA gastroprotective agent, *H2RA* histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor

Table 2. ICD-9-CM codes for peptic ulcers, gastrointestinal procedures, and *Helicobacter pylori* infection

ICD-9-CM codes for PUs
531 gastric ulcer (531.0-531.9)
532 duodenal ulcer (532.0-532.9)
533 peptic ulcer, site unspecified (533.0-533.9)
534 gastrojejunal ulcer (534.0-534.9)
ICD-9-CM codes for gastrointestinal procedures
44.1 diagnostic procedures on stomach (44.11-44.19)
45.1 diagnostic procedures on small intestine (45.11-45.19)
44.4 control of haemorrhage and suture of ulcer of stomach or duodenum
87.62 upper GI series
88.01 computerized axial tomography of abdomen
88.02 other abdomen tomography
ICD-9-CM codes for *H. Pylori* infection
041.86 *H. pylori*

GI gastrointestinal, *ICD-9-CM* international classification of diseases, ninth revision, Clinical modification, *PU* peptic ulcer

475 **Table 3. Dose classification of NSAIDs and H2RAs**

H2RA	Low dose	High dose
ranitidine	<600	≥ 600
famotidine	<80	≥ 80
cimetidine	<1,600	≥ 1,600
NSAID		**Medium/High dose**
diclofenac	<75	≥75
ibuprofen	<1,200	≥1,200
indomethacin	<75	≥75
mefenamic acid	<1,500	≥1,500
naproxen	<500	≥500
piroxicam	<10	≥10
sulindac	<300	≥300

476 Doses are presented in mg/day
477 *H2RA* histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug

Table 4. Patient characteristics by exposure classified according to histamine-2 receptor antagonist dose

		NSAID+low-dose-H2RA	NSAID+high-dose-H2RA
Total		77,509	24,533
H2RA type	Famotidine	77,484 (99.97)	24,532 (100)
	Ranitidine	25 (0.03)	1 (0)
Sex	Male	32,751 (42.3)	10,463 (42.6)
	Female	44,758 (57.7)	14,070 (57.4)
Age in years	Mean (SD)	54 (16.5)	52 (16.4)
Age category (years)	< 65	58,507 (75.5)	19,418 (79.2)
	≥ 65	19,002 (24.5)	5,115 (20.8)
NSAID dose	Low	20,845 (26.9)	7,105 (29.0)
	Medium or high	56,664 (73.1)	17,428 (71.0)
NSAID type	Ibuprofen	15,181 (19.6)	5,644 (23.0)
	Diclofenac	41,193 (53.1)	14,198 (57.9)
	Naproxen	15,941(20.6)	3,240 (13.2)
	Others [a]	5,194 (6.7)	1,451 (5.9)
Concomitant drugs	Corticosteroid	2,617 (3.4)	716 (2.9)
	Anticoagulant	7,223 (9.3)	2,036 (8.3)
	Antiplatelet agent	5,568 (7.2)	1,395 (5.7)
Treatment duration (days)	Mean (SD)	23 (32.1)	18 (28.2)
Treatment duration category (days)	< 30	64,509 (83.2)	21,595 (88.0)
	30-60	6,072 (7.8)	1,397 (5.7)
	> 60	6,928 (8.9)	1,541 (6.3)

Data are presented as n (%) unless otherwise indicated

H2RA histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug, *SD* standard deviation

[a] Others: indomethacin, mefenamic acid, piroxicam, and sulindac

Table 5. Absolute risks and incident rates of peptic ulcer hospitalization in users of non-steroidal anti-inflammatory drug + histamine-2 receptor antagonist

	Low-dose-H2RA	High-dose-H2RA	Total
Number of patients	77,509	24,533	102,042
Number of incident PU cases	64	5	69
Absolute risk (%, 95%CI)	0.08 (0.06 – 0.11)	0.02 (0.01 – 0.05)	0.07 (0.05 – 0.09)
Total patient-years covered	4,819	1,214	6,034
Incidence rate per 1000 patient-years (95%CI)	13.3 (10.4 – 17.0)	4.1 (1.7 – 9.9)	11.4 (9.0 – 14.5)

CI confidence interval, *H2RA* histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug, *PU* peptic ulcer

Table 6. Model details of the risk of peptic ulcer in users of non-steroidal anti-inflammatory drug + histamine-2 receptor antagonist

		Adjusted RR [a] (95% CI)	*P*-value
H2RA dose	**Low**	**1.00**	**-**
	High	**0.32 (0.13 − 0.79)**	**0.014**
H2RA dose (Sensitivity analysis 1[b])	**Low**	**1.00**	**-**
	High	**0.50 (0.31 − 0.82)**	**0.006**
H2RA dose (Sensitivity analysis 2[c])	**Low**	**1.00**	**-**
	High	**0.31 (0.13 − 0.78)**	**0.013**
H2RA dose (Sensitivity analysis 3[d])	**Low**	**1.00**	**-**
	High	**0.33 (0.13 − 0.83)**	**0.019**
Sex	Male	1.00	-
	Female	0.69 (0.43 − 1.11)	0.125
Age	< 65 years	1.00	-
	≥ 65 years	11.84 (6.34 − 22.14)	<.0001
NSAID dose	Low	1.00	-
	Medium or high	1.05 (0.37 − 2.94)	0.927
NSAID type	Ibuprofen	1.00	
	Diclofenac	3.41 (0.83 − 14.00)	0.088
	Naproxen	2.71 (0.60 − 12.25)	0.196
	Others [e]	2.60 (0.61 − 11.16)	0.199
Concomitant drugs	No	1.00	-
	Corticosteroid	1.41 (0.57 − 3.51)	0.460
	Anticoagulant	0.93 (0.43 − 2.04)	0.866
	Antiplatelet agent	1.85 (1.08 − 3.17)	0.026
Treatment duration category	< 30 days	1.00	
	30-60 days	3.94 (2.06 − 7.55)	<.0001
	> 60 days	4.76 (2.75 − 8.23)	<.0001

CI confidence interval, *GI* gastrointestinal, *H2RA* histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug, *PU* peptic ulcer, *RR* relative risk

a Estimates adjusted for age; sex; NSAID dose; NSAID type; concomitant use of corticosteroid, anticoagulant, or antiplatelet agent; treatment duration

b The follow-up period was extended for 30 days

c Any PU diagnosis was included as an outcome instead of restricting them to diagnosis during hospitalization

d Any PU diagnosis without confirmation with GI endoscopy, GI surgery, or related diagnostic procedures was excluded

e Others: indomethacin, mefenamic acid, piroxicam, and sulindac

Figures

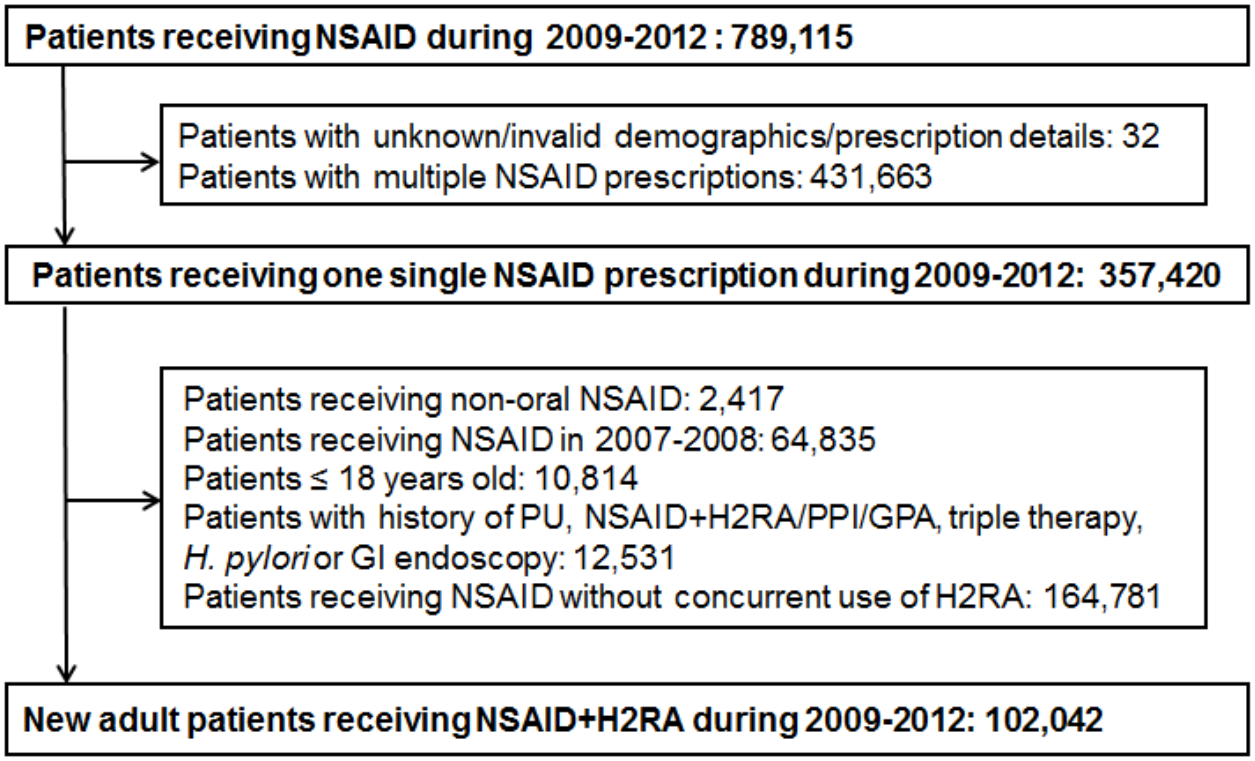

Figure 1. Illustration of patient inclusion/exclusion

GPA gastroprotective agent, *H. Pylori* Helicobacter pylori, *H2RA* histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *PU* peptic ulcer

Supplementary Table 1. Subgroup analysis of the risk of peptic ulcer in users of non-steroidal anti-inflammatory drug+ histamine-2 receptor antagonist

Subgroups	PU case/Patient number		Unadjusted RR (95% CI) (High vs Low)	P-Value
	High-dose-H2RA	Low-dose-H2RA		
Age ≥ 65 years	5 / 5,115	51 / 19,002	0.36 (0.15 – 0.91)	0.022
30-60 days treatment	1 / 1,397	12 / 6,072	0.36 (0.05 – 2.78)	0.484
> 60 days treatment	2 / 1,541	21 / 6,928	0.43 (0.10 – 1.82)	0.413

CI confidence interval, *H2RA* histamine-2 receptor antagonist, *NSAID* non-steroidal anti-inflammatory drugs, *PU* peptic ulcer, *RR* relative risk